TEMOZOLOMIDE- temozolomide capsule
Accord Healthcare Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TEMOZOLOMIDE CAPSULES safely and effectively. See full prescribing information for TEMOZOLOMIDE CAPSULES.

TEMOZOLOMIDE capsules, for oral use

Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Warnings and Precautions (5.5)	11/2019

INDICATIONS AND USAGE

Temozolomide is an alkylating drug indicated for the treatment of adult patients with:

- Newly diagnosed glioblastoma concomitantly with radiotherapy and then as maintenance treatment. (1.1)
- Refractory anaplastic astrocytoma who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine. (1.2)

DOSAGE AND ADMINISTRATION

- Administer either orally or intravenously.
- Newly Diagnosed Glioblastoma:
  - 75 mg/m ^{2} once daily for 42 days concomitant with focal radiotherapy followed by initial maintenance dose of 150 mg/m ^{2} once daily for Days 1 to 5 of each 28-day cycle for 6 cycles. May increase maintenance dose to 200 mg/m ^{2} for cycles 2 to 6 based on toxicity. (2.1)
  - Provide Pneumocystis Pneumonia (PCP) prophylaxis during concomitant phase and continue in patients who develop lymphopenia until resolution to grade 1 or less. (2.1)
- Refractory Anaplastic Astrocytoma: Initial dose of 150 mg/m ^{2} once daily on Days 1 to 5 of each 28-day cycle. (2.2)

DOSAGE FORMS AND STRENGTHS

- Capsules: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg (3)

CONTRAINDICATIONS

- History of hypersensitivity to temozolomide or any other ingredients in temozolomide and dacarbazine. (4.1)

WARNINGS AND PRECAUTIONS

- Myelosuppression: Monitor absolute neutrophil count (ANC) and platelet count prior to each cycle and during treatment. Geriatric patients and women have a higher risk of developing myelosuppression. (5.1)
- Myelodysplastic Syndrome and Secondary Malignancies, including myeloid leukemia, have been observed. (5.2)
- Pneumocystis Pneumonia (PCP): Closely monitor all patients, particularly those receiving steroids, for the development of lymphopenia and PCP. (5.3)
- Hepatotoxicity: Fatal and severe hepatotoxicity have been reported. Perform liver tests at baseline, midway through the first cycle, prior to each subsequent cycle, and approximately 2 to 4 weeks after the last dose of temozolomide (5.4)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. Advise male patients with pregnant partners or female partners of reproductive potential to use condoms. (5.5, 8.1, 8.3)

ADVERSE REACTIONS

- The most common adverse reactions (≥20% incidence) are: alopecia, fatigue, nausea, vomiting, headache, constipation, anorexia, and convulsions. (6.1)
- The most common Grade 3 to 4 hematologic laboratory abnormalities (≥10% incidence) in patients with anaplastic astrocytoma are: decreased lymphocytes, decreased platelets, decreased neutrophils, and decreased leukocytes. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Accord Healthcare Inc., at 1-866-941-7875 or *www.accordhealthcare.us* or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Newly Diagnosed Glioblastoma

Temozolomide capsule is indicated for the treatment of adult patients with newly diagnosed glioblastoma concomitantly with radiotherapy and then as maintenance treatment.

1.2 Refractory Anaplastic Astrocytoma

Temozolomide capsule is indicated for the treatment of adult patients with refractory anaplastic astrocytoma who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Dosage Modifications for Newly Diagnosed Glioblastoma

Administer temozolomide capsules either orally or intravenously once daily for 42 consecutive days during the concomitant phase with focal radiotherapy and then once daily on Days 1 to 5 of each 28-day cycle for 6 cycles during the maintenance phase.

Provide Pneumocystis pneumonia (PCP) prophylaxis during the concomitant phase and continue in patients who develop lymphocytopenia until resolution to grade 1 or less *[see Warnings and Precautions (5.3)]* .

Concomitant Phase

The recommended dosage of temozolomide capsules is 75 mg/m ^{2} orally once daily for 42 days (up to 49 days) concomitant with focal radiotherapy (60 Gy administered in 30 fractions). Focal radiotherapy includes the tumor bed or resection site with a 2-to 3-cm margin.

Obtain a complete blood count weekly. No dose reductions are recommended during the concomitant phase. The recommended dosage modifications during the concomitant phase are provided in Table 1.

TABLE 1: Temozolomide Dosage Modifications During Concomitant Phase

Adverse Reaction	Interruption	Discontinuation
Absolute Neutrophil Count	Withhold temozolomide if ANC is greater than or equal to 0.5 x 10 ^{9}/L and less than 1.5 x 10 ^{9}/L. Resume temozolomide when ANC is greater than or equal to 1.5 x 10 ^{9}/L.	Discontinue temozolomide if platelet count is less than 0.5 x 10 ^{9}/L.
Platelet Count	Withhold temozolomide if platelet count is greater than or equal to 10 x 10 ^{9}/L and less than 100 x 10 ^{9}/L. Resume temozolomide when platelet count is greater than or equal to 100 x 10 ^{9}/L.	Discontinue temozolomide if platelet count is less than 10 x 10 ^{9}/L.
Non-hematological Adverse Reaction (except for alopecia, nausea, vomiting)	Withhold temozolomide if Grade 2 adverse reaction occurs.	Discontinue temozolomide if Grade 3 or 4 adverse reaction occurs.

	Resume temozolomide when resolution to Grade 1 or less.	

Maintenance Phase

Beginning 4 weeks after Concomitant Phase completion, administer temozolomide either orally or intravenously once daily on Days 1 to 5 of each 28-day cycle for 6 cycles. The recommended dosage of temozolomide is as follows:

- Cycle 1: 150 mg/m ^{2} per day
- Cycles 2 to 6: May increase to 200 mg/m ^{2} per day if the following conditions are met before starting cycle 2. If the dose was not escalated at the onset of Cycle 2, **do not** increase the dose for Cycles 3 to 6.
  - Non-hematologic toxicity is Grade 2 or less (except for alopecia, nausea, vomiting)
  - ANC is greater than or equal to 1.5 x 10 ^{9}/L and
  - Platelet count is greater than or equal to 100 x 10 ^{9}/L.

Obtain a complete blood count on Day 22 and then weekly until the ANC is above 1.5 x 10 ^{9}/L and the platelet count is above 100 x 10 ^{9}/L. Do not start the next cycle until the ANC and platelet count exceed these levels.

The recommended dosage modifications during the maintenance phase are provided in **Table 2**. If Temozolomide is withheld, reduce the dose for the next cycle by 50 mg/m ^{2} per day. Permanently discontinue Temozolomide in patients who are unable to tolerate a dose of 100 mg/m ^{2} per day.

TABLE 2: Temozolomide Dosage Modifications During Maintenance Treatment

Toxicity	Interruption and Dose Reduction	Discontinuation
Absolute Neutrophil Count	Withhold temozolomide if ANC less than 1 x 10 ^{9}/L. When ANC is above 1.5 x 10 ^{9}/L, resume temozolomide at reduced dose for the next cycle.	Unable to tolerate a dose of 100 mg/m ^{2} per day.
Platelet Count	Withhold temozolomide if platelet less than 50 x 10 ^{9}/L. When platelet count is above 100 x 10 ^{9}/L, resume temozolomide at reduced dose for the next cycle.	Unable to tolerate a dose of 100 mg/m ^{2} per day.
Non-hematological Adverse Reaction (except for alopecia, nausea, vomiting)	Withhold temozolomide if Grade 3 adverse reaction. When resolved to grade 1 or less, resume temozolomide at reduced dose for the next cycle.	Recurrent Grade 3 after dose reduction. Grade 4 Unable to tolerate a dose of 100 mg/m ^{2} per day.

2.2 Recommended Dosage and Dosage Modifications for Refractory Anaplastic Astrocytoma

The recommended initial dosage of temozolomide is 150 mg/m ^{2} once daily on Days 1 to 5 of each 28-day cycle. Increase the temozolomide dose to 200 mg/m ^{2} per day if the following conditions are met at the nadir and on Day 1 of the next cycle:

- ANC is greater than or equal to 1.5 x 10 ^{9}/L and
- Platelet count is greater than or equal to 100 x 10 ^{9}/L.

Continue temozolomide until disease progression or unacceptable toxicity. In the clinical trial, treatment could be continued for a maximum of 2 years, but the optimum duration of therapy is not known.

Obtain a complete blood count on Day 22 and then weekly until the ANC is above 1.5 x 10^9/L and the platelet count is above 100 x 10^9/L. Do not start the next cycle until the ANC and platelet count exceed these levels.

If the ANC is less than 1 x 10^9/L or the platelet count is less than 50 x 10^9/L during any cycle, reduce the temozolomide dose for the next cycle by 50 mg/m^2 per day. Permanently discontinue temozolomide in patients who are unable to tolerate a dose of 100 mg/m^2 per day.

2.3 Preparation and Administration

Temozolomide is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Temozolomide capsules

Administer Temozolomide consistently with respect to food (fasting vs. nonfasting) *[see Clinical Pharmacology (12.3)]*. To reduce nausea and vomiting, take temozolomide on an empty stomach or at bedtime and consider antiemetic therapy prior to and/or following temozolomide administration.

Swallow temozolomide capsules whole. Do not open or chew capsules.

If capsules are accidentally opened or damaged, take precautions to avoid inhalation or contact with the skin or mucous membranes. In case of powder contact, the hands should be washed.

3 DOSAGE FORMS AND STRENGTHS

- Temozolomide capsules, USP for oral administration
  - 5-mg capsules have white bodies with green caps. The capsule body is imprinted with '5'. The cap is imprinted with 'TMZ'.
  - 20-mg capsules have white bodies with yellow caps. The capsule body is imprinted with '20'. The cap is imprinted with 'TMZ'.
  - 100-mg capsules have white bodies with pink caps. The capsule body is imprinted with '100'. The cap is imprinted with 'TMZ'.
  - 140-mg capsules have white bodies with transparent blue caps. The capsule body is imprinted with '140'. The cap is imprinted with 'TMZ'.
  - 180-mg capsules have white bodies with maroon caps. The capsule body is imprinted with '180'. The cap is imprinted with 'TMZ'.
  - 250-mg capsules have white bodies with white caps. The capsule body is imprinted with '250'. The cap is imprinted with 'TMZ'.

4 CONTRAINDICATIONS

Temozolomide is contraindicated in patients with a history of hypersensitivity reactions to:

- temozolomide or any other ingredients in temozolomide; and
- dacarbazine, since both temozolomide and dacarbazine are metabolized to the same active metabolite 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide.

Reactions to Temozolomide have included anaphylaxis *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Myelosuppression, including pancytopenia, leukopenia and anemia, some with fatal outcomes, have

occurred with temozolomide *[see Adverse Reactions (6.1, 6.2)]*. Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression.

Prior to dosing, patients must have an ANC of 1.5 x 10^9/L or greater and a platelet count of 100 x 10^9/L or greater.

For the concomitant phase with radiotherapy, obtain a complete blood count prior to initiation of treatment and weekly during treatment *[see Dosage and Administration (2.1)]*.

For the 28-day treatment cycles, obtain a complete blood count prior to treatment on Day 1 and on Day 22 of each cycle. Perform complete blood counts weekly until recovery if the ANC falls below 1.5 x 10^9/L and the platelet count falls below 100 x 10^9/L *[see Dosage and Administration (2.1, 2.2)]*.

5.2 Myelodysplastic Syndrome and Secondary Malignancies

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been observed following temozolomide administration.

5.3 Pneumocystis Pneumonia

Pneumocystis pneumonia (PCP) can occur in patients receiving temozolomide. The risk of PCP is increased in patients receiving steroids or with longer treatment regimens.

For patients with newly diagnosed glioblastoma, provide PCP prophylaxis for all patients during the concomitant phase. Continue in patients who experience lymphopenia until resolution to grade 1 or less *[see Dosage and Administration (2.1)]*.

Monitor all patients receiving temozolomide for the development of lymphopenia and PCP.

5.4 Hepatotoxicity

Fatal and severe hepatotoxicity have been reported in patients receiving temozolomide. Perform liver tests at baseline, midway through the first cycle, prior to each subsequent cycle, and approximately two to four weeks after the last dose of temozolomide.

5.5 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, temozolomide can cause fetal harm when administered to a pregnant woman. Adverse developmental outcomes have been reported in both pregnant patients and pregnant partners of male patients. Oral administration of temozolomide to rats and rabbits during the period of organogenesis resulted in embryolethality and polymalformations at doses less than the maximum human dose based on body surface area.

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with temozolomide and for at least 6 months after the final dose. Because of potential risk of genotoxic effects on sperm, advise male patients with female partners of reproductive potential to use condoms during treatment with temozolomide and for at least 3 months after the final dose. Advise male patients not to donate semen during treatment with temozolomide and for at least 3 months after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression *[see Warnings and Precautions (5.1)]* .
- Myelodysplastic Syndrome and Secondary Malignancies *[see Warnings and Precautions (5.2)]* .
- Pneumocystis Pneumonia *[see Warnings and Precautions (5.3)]* .
- Hepatotoxicity *[see Warnings and Precautions (5.4)]* .

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Newly Diagnosed Glioblastoma

The safety of temozolomide was evaluated in Study MK-7365-051 *[see Clinical Studies (14.1)]* .

Forty-nine percent (49%) of patients treated with temozolomide reported one or more severe or life-threatening reactions, most commonly fatigue (13%), convulsions (6%), headache (5%), and thrombocytopenia (5%).

The most common adverse reactions (≥20%) across the cumulative temozolomide experience were alopecia, fatigue, nausea, and vomiting. Table 3 summarizes the adverse reactions in Newly Diagnosed Glioblastoma Trial. Overall, the pattern of reactions during the maintenance phase was consistent with the known safety profile of temozolomide.

TABLE 3: Adverse Reactions (≥5%) in Patients Receiving temozolomide in Newly Diagnosed Glioblastoma Trial

Adverse Reactions	Concomitant Phase				Maintenance Phase	
	Radiation Therapy and Temozolomide N=288*		Radiation Therapy Alone N=285		Temozolomide N=224	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Skin and Subcutaneous Tissue						
Alopecia	69		63		55	
Rash	19	1	15		13	1
Dry Skin	2		2		5	<1
Pruritus	4		1		5	
Erythema	5		5		1	
General						
Fatigue	54	7	49	5	61	9
Anorexia	19	1	9	<1	27	1
Headache	19	2	17	4	23	4
Weakness	3	2	3	1	7	2
Dizziness	4	1	4		5	
Gastrointestinal System						
Nausea	36	1	16	<1	49	1
Vomiting	20	<1	6	<1	29	2
Constipation	18	1	6		22	
Diarrhea	6		3		10	1
Stomatitis	7		5	<1	9	1
Abdominal Pain	2	<1	1		5	<1
Eye						
Vision Blurred	9	1	9	1	8	
Injury						
Radiation Injury NOS	7		4	<1	2	
Central and Peripheral Nervous System						
Convulsions	6	3	7	3	11	3
Memory Impairment	3	<1	4	<1	7	1

Confusion	4	1	4	2	5	2
Special Senses Other						
Taste Perversion	6		2		5	
Respiratory System						
Coughing	5	1	1		8	<1
Dyspnea	4	2	3	1	5	<1
Psychiatric						
Insomnia	5		3	<1	4	
Immune System						
Allergic Reaction	5		2	<1	3	
Platelet, Bleeding and Clotting						
Thrombocytopenia	4	3	1		8	4
Musculoskeletal System						
Arthralgia	2	<1	1		6	

*One patient who was randomized to radiation therapy only arm received radiation therapy and Temozolomide.

NOS=not otherwise specified.

Note: Grade 5 (fatal) adverse reactions are included in the Grade ≥3 column.

When laboratory abnormalities and adverse reactions were combined, Grade 3 or Grade 4 neutrophil abnormalities including neutropenic reactions were observed in 8% of the patients, and Grade 3 or Grade 4 platelet abnormalities including thrombocytopenic reactions, were observed in 14% of patients.

Refractory Anaplastic Astrocytoma:

The safety of temozolomide was evaluated in Study MK-7365-006 *[see Clinical Studies (14.2)]* .

Myelosuppression (thrombocytopenia and neutropenia) was the dose-limiting adverse reaction. It usually occurred within the first few cycles of therapy and was not cumulative. Myelosuppression occurred late in the treatment cycle and returned to normal, on average, within 14 days of nadir counts. The median nadirs occurred at 26 days for platelets (range: 21 to 40 days) and 28 days for neutrophils (range: 1 to 44 days). Only 14% (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had a platelet nadir, which may have delayed the start of the next cycle. Less than 10% of patients required hospitalization, blood transfusion, or discontinuation of therapy due to myelosuppression.

The most common adverse reactions (≥20%) were nausea, vomiting, headache, fatigue, constipation, and convulsions.

Tables 4 and **5** summarize the adverse reactions and hematological laboratory abnormalities in Refractory Anaplastic Astrocytoma Trial.

TABLE 4: Adverse Reactions (≥5%) in Patients Receiving Temozolomide in Refractory Anaplastic Astrocytoma Trial

Adverse Reactions	Temozolomide N=158	
	All Reactions (%)	Grade 3 to 4 (%)
Gastrointestinal System		
Nausea	53	10
Vomiting	42	6
Constipation	33	1

Diarrhea	16	2
Abdominal Pain	9	1
Anorexia	9	1
General		
Headache	41	6
Fatigue	34	4
Asthenia	13	6
Fever	13	2
Back Pain	8	3
Central and Peripheral Nervous System		
Convulsions	23	5
Hemiparesis	18	6
Dizziness	12	1
Coordination abnormal	11	1
Amnesia	10	4
Insomnia	10	
Paresthesia	9	1
Somnolence	9	3
Paresis	8	3
Urinary incontinence	8	2
Ataxia	8	2
Dysphasia	7	1
Convulsions local	6	
Gait abnormal	6	1
Confusion	5	
Cardiovascular		
Edema peripheral	11	1
Resistance Mechanism		
Infection viral	11	
Endocrine		
Adrenal hypercorticism	8	
Respiratory System		
Upper respiratory tract infection	8	
Pharyngitis	8	
Sinusitis	6	
Coughing	5	
Skin and Appendages		
Rash	8	
Pruritus	8	1
Urinary System		
Urinary tract infection	8	
Micturition increased frequency	6	
Psychiatric Disorders		
Anxiety	7	1
Depression	6	
Reproductive Disorders		
Breast pain, female	6	
Metabolic		

Weight increase	5	
Musculoskeletal System		
Myalgia	5	
Vision		
Diplopia	5	
Vision abnormal*	5	

*This item includes blurred vision; visual deficit; vision changes; and vision troubles.

TABLE 5: Grade 3 to 4 Adverse Hematologic Laboratory Abnormalities in Refractory Anaplastic Astrocytoma Trial

	Temozolomide *†
Decreased lymphocytes	55%
Decreased platelets	19%
Decreased neutrophils	14%
Decreased leukocytes	11%
Decreased hemoglobin	4%

* Change from Grade 0 to 2 at baseline to Grade 3 or 4 during treatment.

† Dominator range = 142, 158

Hematological Toxicities for Advanced Gliomas:

In clinical trial experience with 110 to 111 females and 169 to 174 males (depending on measurements), females experienced higher rates of Grade 4 neutropenia (ANC < 0.5 x 10^9/L) and thrombocytopenia (< 20 x 10^9/L) than males in the first cycle of therapy (12% vs. 5% and 9% vs. 3%, respectively).

In the entire safety database for which hematologic data exist (N=932), 7% (4/61) and 9.5% (6/63) of patients > 70 years experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. For patients ≤ 70 years, 7% (62/871) and 5.5% (48/879) experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. Pancytopenia, leukopenia, and anemia also occurred.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of temozolomide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the drug exposure.

Dermatologic: Toxic epidermal necrolysis and Stevens-Johnson syndrome

Immune System: Hypersensitivity reactions, including anaphylaxis. Erythema multiforme, which resolved after discontinuation of temozolomide capsules and, in some cases, recurred upon rechallenge.

Hematopoietic: Prolonged pancytopenia, which may result in aplastic anemia and fatal outcomes.

Hepatobiliary: Fatal and severe hepatotoxicity, elevation of liver enzymes, hyperbilirubinemia, cholestasis, and hepatitis.

Infections: Serious opportunistic infections, including some cases with fatal outcomes with bacterial, viral (primary and reactivated), fungal, and protozoan organisms.

Pulmonary: Interstitial pneumonitis, pneumonitis, alveolitis, and pulmonary fibrosis.

Endocrine: Diabetes insipidus

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1)]* and findings from animal studies, temozolomide can cause fetal harm when administered to a pregnant woman. Available postmarketing reports describe cases of spontaneous abortions and congenital malformations, including polymalformations with central nervous system, facial, cardiac, skeletal, and genitourinary system anomalies with exposure to temozolomide during pregnancy. These cases report similar adverse developmental outcomes to those observed in animal studies. Administration of temozolomide to rats and rabbits during the period of organogenesis caused numerous external, internal, and skeletal malformations at doses less than the maximum human dose based on body surface area (see Data). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Five consecutive days of oral administration of temozolomide at doses of 75 and 150 mg/m ^{2} (0.38 and 0.75 times the human dose of 200 mg/m ^{2}) in rats and rabbits, respectively, during the period of organogenesis (Gestation Days 8 to 12) caused numerous malformations of the external and internal organs and skeleton in both species. In rabbits, temozolomide at the 150 mg/m ^{2} dose (0.75 times the human dose of 200 mg/m ^{2}) caused embryolethality as indicated by increased resorptions.

8.2 Lactation

There are no data on the presence of temozolomide or its metabolites in human milk, the effects on a breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions, including myelosuppression from temozolomide in the breastfed children, advise women not to breastfeed during treatment with temozolomide and for at least 1 week after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating temozolomide *[see Use in Specific Population (8.1)]*.

Contraception

Females

Temozolomide can cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Population (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with temozolomide and for at least 6 months after the last dose.

Males

Because of the potential for embryofetal toxicity and genotoxic effects on sperm cells, advise male patients with pregnant partners or female partners of reproductive potential to use condoms during treatment with temozolomide and for at least 3 months after the final dose *[see Use in Specific Population (8.1), Nonclinical Toxicology (13.1)]*. Advise male patients not to donate semen during treatment with temozolomide and for at least 3 months after the final dose.

Infertility

Temozolomide may impair male fertility *[see Nonclinical Toxicology (13.1)]* . Limited data from male patients show changes in sperm parameters during treatment with temozolomide; however, no information is available on the duration or reversibility of these changes.

8.4 Pediatric Use

Safety and effectiveness of temozolomide have not been established in pediatric patients. Safety and effectiveness of temozolomide capsules were assessed, but not established, in 2 open-label studies in pediatric patients aged 3 to18 years. In one study, 29 patients with recurrent brain stem glioma and 34 patients with recurrent high-grade astrocytoma were enrolled. In a second study conducted by the Children's Oncology Group (COG), 122 patients were enrolled, including patients with medulloblastoma/PNET (29), high grade astrocytoma (23), low grade astrocytoma (22), brain stem glioma (16), ependymoma (14), other CNS tumors (9), and non-CNS tumors (9). The adverse reaction profile in pediatric patients was similar to adults.

8.5 Geriatric Use

In the Newly Diagnosed Glioblastoma trial, Study MK-7365-051, 15% of patients were 65 years and older. This study did not include sufficient numbers of patients aged 65 years and older to determine differences in effectiveness from younger patients. No overall differences in safety were observed between patients ≥65 years and younger patients.

In the Refractory Anaplastic Astrocytoma trial, Study MK-7365-0006, 4% of patients were 70 years and older. This study did not include sufficient numbers of patients aged 70 years and older to determine differences in effectiveness from younger patients. Patients 70 years and older had a higher incidence of Grade 4 neutropenia (25%) and Grade 4 thrombocytopenia (20%) in the first cycle of therapy than patients less than 70 years of age *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

8.6 Renal Impairment

No dosage adjustment is recommended for patients with creatinine clearance (CLcr) of 36 to 130 mL/min/m^2 *[see Clinical Pharmacology (12.3)]*. The recommended dose of temozolomide has not been established for patients with severe renal impairment (CLcr < 36 mL/min/m^2) or for patients with end-stage renal disease on dialysis.

8.7 Hepatic Impairment

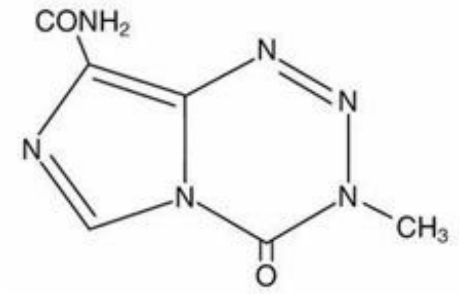
No dosage adjustment is recommended for patients with mild to moderate hepatic impairment (Child Pugh class A and B) *[see Clinical Pharmacology (12.3)]*. The recommended dose of temozolomide has not been established for patients with severe hepatic impairment (Child-Pugh class C).

10 OVERDOSAGE

Dose-limiting toxicity was myelosuppression and was reported with any dose but is expected to be more severe at higher doses. An overdose of 2000 mg per day for 5 days was taken by one patient and the adverse reactions reported were pancytopenia, pyrexia, multi-organ failure, and death. There are reports of patients who have taken more than 5 days of treatment (up to 64 days), with adverse reactions reported including myelosuppression, which in some cases was severe and prolonged, and infections and resulted in death. In the event of an overdose, monitor complete blood count and provide supportive measures as necessary.

11 DESCRIPTION

Temozolomide is an alkylating drug. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1d]- *as*-tetrazine-8-carboxamide. The structural formula of temozolomide is:



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_6O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5) and labile at pH >7; hence temozolomide can be administered orally. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

Temozolomide capsules, USP

Temozolomide capsules, USP for oral use contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of temozolomide.

The inactive ingredients are as follows:

Temozolomide capsules USP 5 mg: lactose anhydrous (168 mg), colloidal anhydrous silica (1 mg), sodium starch glycolate (16 mg), tartaric acid (7 mg), and stearic acid (3 mg).

Temozolomide capsules USP 20 mg: lactose anhydrous (14.6 mg), colloidal anhydrous silica (0.2 mg), sodium starch glycolate (3.2 mg), tartaric acid (1.4 mg), and stearic acid (0.6 mg).

Temozolomide capsules USP 100 mg: lactose anhydrous (73 mg), colloidal anhydrous silica (1 mg), sodium starch glycolate (16 mg), tartaric acid (7 mg), and stearic acid (3 mg).

Temozolomide capsules USP 140 mg: lactose anhydrous (102.2 mg), colloidal anhydrous silica (1.4 mg), sodium starch glycolate (22.4 mg), tartaric acid (9.8 mg), and stearic acid (4.2 mg).

Temozolomide capsules USP 180 mg: lactose anhydrous (131.4 mg), colloidal anhydrous silica (1.8 mg), sodium starch glycolate (28.8 mg), tartaric acid (12.6 mg), and stearic acid (5.4 mg).

Temozolomide capsules USP 250 mg: lactose anhydrous (182.5 mg), colloidal anhydrous silica (2.5 mg), sodium starch glycolate (40 mg), tartaric acid (17.5 mg), and stearic acid (7.5 mg).

The body of the capsules is made of gelatin, and is white. The body of 250 mg capsule contain additionally sodium lauryl sulfate. The cap is also made of gelatin, and the colors vary based on the dosage strength. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains black iron oxide, potassium hydroxide and shellac.

Temozolomide capsules USP 5 mg: The green cap contains gelatin, titanium dioxide, iron oxide yellow and FD&C Blue 2.

Temozolomide capsules USP 20 mg: The yellow cap contains gelatin, titanium dioxide and iron oxide yellow.

Temozolomide capsules USP 100 mg: The pink cap contains gelatin, titanium dioxide and iron oxide red.

Temozolomide capsules USP 140 mg: The transparent blue cap contains gelatin and FD&C Blue 2.

Temozolomide capsules USP 180 mg: The maroon cap contains gelatin, iron oxide red, iron oxide yellow and titanium dioxide.

Temozolomide capsules USP 250 mg: The white cap contains gelatin, titanium dioxide and sodium lauryl sulfate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine.

12.3 Pharmacokinetics

Following a single oral dose of 150 mg/m^2, the mean C_{max} value for temozolomide was 7.5 mcg/mL and for MTIC was 282 ng/mL. The mean AUC value for temozolomide was 23.4 mcg·hr/mL and for MTIC was 864 ng·hr/mL.

Following a single 90-minute intravenous infusion of 150 mg/m^2, the mean C_{max} value for temozolomide was 7.3 mcg/mL and for MTIC was 276 ng/mL. The mean AUC value for temozolomide was 24.6 mcg·hr/mL and for MTIC was 891 ng·hr/mL.

Temozolomide exhibits linear kinetics over the therapeutic dosing range of 75 mg/m^2/day to 250 mg/m^2/day.

Absorption

The median T_{max} is 1 hour.

Effect of Food

The mean C_{max} and AUC decreased by 32% and 9%, respectively, and median Tmax increased by 2-fold (from 1 to 2.25 hours) when temozolomide capsules were administered after a modified high-fat breakfast (587 calories comprised of 1 fried egg, 2 strips of bacon, 2 slices of toast, 2 pats of butter, and 8 oz whole milk).

Distribution

Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). The mean percent bound of drug-related total radioactivity is 15%.

Elimination

Clearance of temozolomide is about 5.5 L/hr/m^2 and the mean elimination half-life is 1.8 hours.

Metabolism

Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, MTIC and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively.

Excretion

About 38% of the administered temozolomide total radioactive dose is recovered over 7 days: 38% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is unchanged temozolomide (6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%).

Specific Populations

No clinically meaningful differences in the pharmacokinetics of temozolomide were observed based on age (range: 19 to 78 years), gender, smoking status (smoker vs. non-smoker), creatinine clearance (CLcr) of 36 to 130 mL/min/m^2, or mild to moderate hepatic impairment (Child Pugh class A and B).

The pharmacokinetics of temozolomide has not been studies in patients with CLcr < 36 mL/min/m^2, end-stage renal disease on dialysis, or severe hepatic impairment (Child Pugh class C).

Drug Interaction Studies

Effect of Other Drugs on Temozolomide Pharmacokinetics

In a multiple-dose study, administration of Temozolomide capsules with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC.

A population analysis indicated that administration of valproic acid decreases the clearance of temozolomide by about 5%.

A population analysis did not demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, histamine-2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Temozolomide is carcinogenic in rats at doses less than the maximum recommended human dose. Temozolomide induced mammary carcinomas in both males and females at doses 0.13 to 0.63 times the maximum human dose (25 to 125 mg/m^2) when administered orally on 5 consecutive days every 28 days for 6 cycles. Temozolomide also induced fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate, carcinomas of the seminal vesicles, schwannomas of the heart, optic nerve, and harderian gland, and adenomas of the skin, lung, pituitary, and thyroid at doses 0.5 times the maximum daily dose. Mammary tumors were also induced following 3 cycles of temozolomide at the maximum recommended daily dose.

Temozolomide is a mutagen and a clastogen. In a reverse bacterial mutagenesis assay (Ames assay), temozolomide increased revertant frequency in the absence and presence of metabolic activation. Temozolomide was clastogenic in human lymphocytes in the presence and absence of metabolic activation.

Temozolomide impairs male fertility. Temozolomide caused syncytial cells/immature sperm formation at doses 50 and 125 mg/m^2 (0.25 and 0.63 times the human dose of 200 mg/m^2) in rats and dogs, respectively, and testicular atrophy in dogs at 125 mg/m^2.

13.2 Animal Toxicology and/or Pharmacology

Toxicology studies in rats and dogs identified a low incidence of hemorrhage, degeneration, and necrosis of the retina at temozolomide doses equal to or greater than 125 mg/m^2 (0.63 times the human dose of 200 mg/m^2). These changes were most commonly seen at doses where mortality was observed.

14 CLINICAL STUDIES

14.1 Newly Diagnosed Glioblastoma

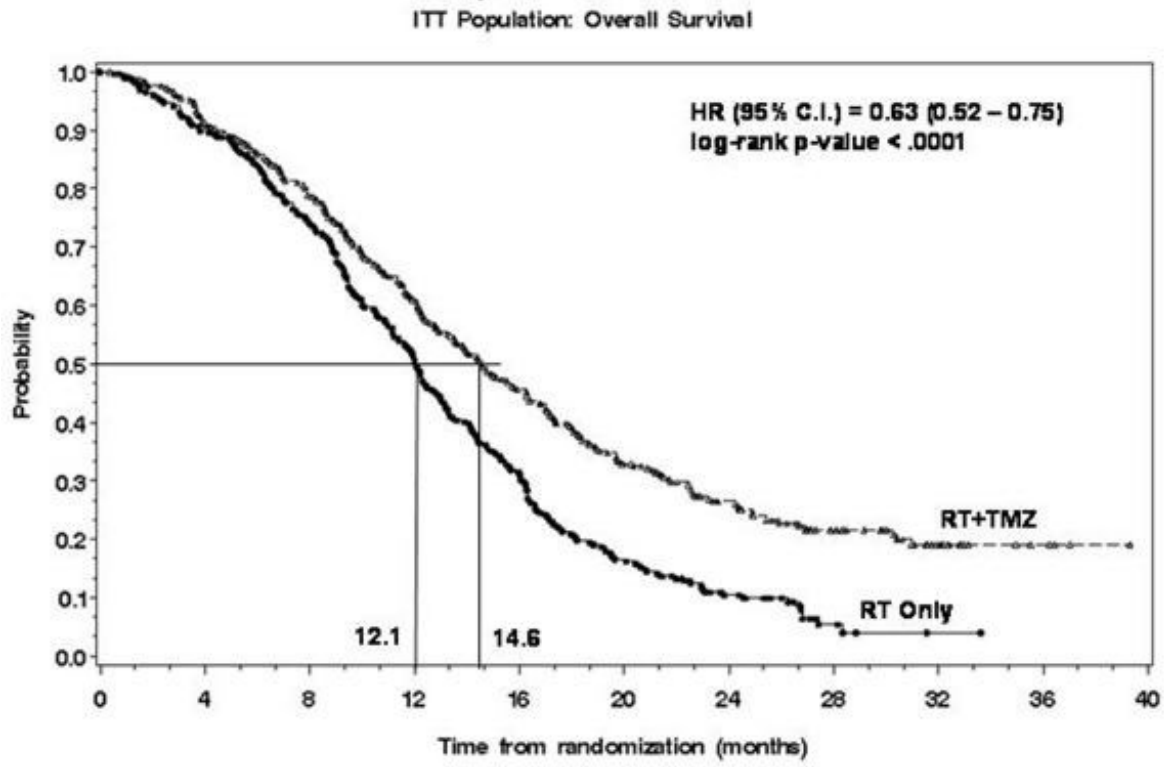
The efficacy of temozolomide was evaluated in Study MK-7365-051, a randomized (1:1), multicenter, open-label trial. Eligible patients were required to have newly diagnosed glioblastoma. Patients were randomized to receive either radiation therapy alone or concomitant temozolomide 75 mg/m^2 once daily starting the first day of radiation therapy and continuing until the last day of radiation therapy for 42 days (with a maximum of 49 days), followed by temozolomide 150 mg/m^2 or 200 mg/m^2 once daily on Days 1 to 5 of each 28-day cycle, starting 4 weeks after the end of radiation therapy and continuing for 6 cycles. In both arms, focal radiation therapy was delivered as 60 Gy/30 fractions and included radiation to the tumor bed or resection site with a 2-to 3-cm margin. PCP prophylaxis was required during the concomitant phase, regardless of lymphocyte count and continued until recovery of lymphocyte count to

grade 1 or less. The major efficacy outcome measure was overall survival.

A total of 573 patients were randomized, 287 to temozolomide and radiation therapy and 286 to radiation therapy alone. At the time of disease progression, temozolomide was administered as salvage therapy in 161 patients of the 282 (57%) in the radiation therapy alone arm and 62 patients of the 277 (22%) in the temozolomide and radiation therapy arm.

The addition of concomitant and maintenance temozolomide to radiation therapy for the treatment of patients with newly diagnosed glioblastoma showed a statistically significant improvement in overall survival compared to radiotherapy alone **(Figure 1)**. The hazard ratio (HR) for overall survival was 0.63 (95% CI: 0.52, 0.75) with a log-rank P<0.0001 in favor of the temozolomide arm. The median survival was increased by 2.5 months in the temozolomide arm.

FIGURE 1: Kaplan-Meier Curves for Overall Survival (ITT Population) in Newly Diagnosed Glioblastoma Trial



14.2 Refractory Anaplastic Astrocytoma

The efficacy of temozolomide was evaluated in Study MK-7365-006, a single-arm, multicenter trial. Eligible patients had anaplastic astrocytoma at first relapse and a baseline Karnofsky performance status (KPS) of 70 or greater. Patients had previously received radiation therapy and may also have previously received a nitrosourea with or without other chemotherapy. Fifty-four patients had disease progression on prior therapy with both a nitrosourea and procarbazine and their malignancy was considered refractory to chemotherapy (refractory anaplastic astrocytoma population). Temozolomide capsules were given on Days 1 to 5 of each 28-day cycle at a starting dose of 150 mg/m ^{2}/day. If ANC was ≥1.5 x 10 ^{9}/L and platelet count was ≥100 x 10 ^{9}/L at the nadir and on Day 1 of the next cycle, the temozolomide dose was increased to 200 mg/m ^{2}/day. The major efficacy outcome measure was progression-free survival at 6 months and the additional efficacy outcome measures were overall survival and overall response rate.

In the refractory anaplastic astrocytoma population (n=54), the median age was 42 years (range: 19 to 76); 65% were male; and 72% had a KPS of >80. Sixty-three percent of patients had surgery other than a biopsy at the time of initial diagnosis. Of those patients undergoing resection, 73% underwent a subtotal resection and 27% underwent a gross total resection. Eighteen percent of patients had surgery at the

time of first relapse. The median time from initial diagnosis to first relapse was 13.8 months (range: 4.2 months to 6.3 years).

In the refractory anaplastic astrocytoma population, the overall response rate (CR+PR) was 22% (12 of 54 patients) and the complete response rate was 9% (5 of 54 patients). The median duration of all responses was 50 weeks (range: 16 to 114 weeks) and the median duration of complete responses was 64 weeks (range: 52 to 114 weeks). In this population, progression-free survival at 6 months was 45% (95% CI: 31%, 58%) and progression-free survival at 12 months was 29% (95% CI: 16%, 42%). Median progression-free survival was 4.4 months. Overall survival at 6 months was 74% (95% CI: 62%, 86%) and 12-month overall survival was 65% (95% CI: 52%, 78%). Median overall survival was 15.9 months.

15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.

16 HOW SUPPLIED/STORAGE AND HANDLING

Temozolomide is a cytotoxic drug. Follow applicable special handling and disposal procedures. [1]

Temozolomide capsules, USP

Temozolomide capsules, USP are supplied in amber glass bottles with child-resistant polypropylene caps and child-resistant sachet packs containing the following capsule strengths:

Temozolomide Capsules USP 5 mg: have white bodies with green caps. The capsule body is imprinted with '5'. The cap is imprinted with 'TMZ'.
They are supplied as follows:
Amber Glass Bottles
5 count – NDC 16729-048-53
14 count – NDC 16729-048-54
Sachet Packs (Carton Contains Individual Sachet with One Capsule each):
5 count – NDC 16729-048-31
14 count – NDC 16729-048-04

Temozolomide Capsules USP 20 mg: have white bodies with yellow caps. The capsule body is imprinted with '20'. The cap is imprinted with 'TMZ'.
They are supplied as follows:
Amber Glass Bottles
5 count – NDC 16729-049-53
14 count – NDC 16729-049-54
Sachet Packs (Carton Contains Individual Sachet with One Capsule each):
5 count – NDC 16729-049-31
14 count – NDC 16729-049-04

Temozolomide Capsules USP 100 mg: have white bodies with pink caps. The capsule body is imprinted with '100'. The cap is imprinted with 'TMZ'.
They are supplied as follows:
Amber Glass Bottles
5 count – NDC 16729-050-53
14 count – NDC 16729-050-54
Sachet Packs (Carton Contains Individual Sachet with One Capsule each):
5 count – NDC 16729-050-31
14 count – NDC 16729-050-04

Temozolomide Capsules USP 140 mg: have white bodies with transparent blue caps. The capsule body is imprinted with '140'. The cap is imprinted with 'TMZ'.
They are supplied as follows:

Amber Glass Bottles
5 count – NDC 16729-129-53
14 count – NDC 16729-129-54
Sachet Packs (Carton Contains Individual Sachet with One Capsule each):
5 count – NDC 16729-129-31
14 count – NDC 16729-129-04

Temozolomide Capsules USP 180 mg: have white bodies with maroon caps. The capsule body is imprinted with '180'. The cap is imprinted with 'TMZ'.
They are supplied as follows:
Amber Glass Bottles
5 count – NDC 16729-130-53
14 count – NDC 16729-130-54
Sachet Packs (Carton Contains Individual Sachet with One Capsule each):
5 count – NDC 16729-130-31
14 count – NDC 16729-130-04

Temozolomide Capsules USP 250 mg: have white bodies with white caps. The capsule body is imprinted with '250'. The cap is imprinted with 'TMZ'.
They are supplied as follows:
Amber Glass Bottles
5 count – NDC 16729-051-53
Sachet Packs (Carton Contains Individual Sachet with One Capsule each):
5 count – NDC 16729-051-31

Store temozolomide capsules, USP at 25°C (77°F) [see USP Controlled Room Temperature]; excursions permitted to 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression
Inform patients that temozolomide can cause low blood cell counts and the need for frequent monitoring of blood cell counts. Advise patients to contact their healthcare provider immediately for bleeding, fever, or other signs of infection *[see Warnings and Precautions (5.1)]* .

Myelodysplastic Syndrome and Secondary Malignancies
Advise patients of the increased risk of myelodysplastic syndrome and secondary malignancies *[see Warnings and Precautions (5.2)]* .

Pneumocystis Pneumonia
Advise patients of the increased risk of Pneumocystis pneumonia and to contact their healthcare provided immediately for new or worsening pulmonary symptoms. Inform patients that prophylaxis for Pneumocystis pneumonia may be needed *[see Dosage and Administration (2.1), Warnings and Precautions (5.3)]* .

Hepatotoxicity
Advise patients of the increased risk of hepatotoxicity and to contact their healthcare provider immediately for signs or symptoms of hepatoxicity *[see Warnings and Precautions (5.4)]* .

Administration Instructions
Advise patient to not open capsules. If capsules are accidentally opened or damaged, advise patients to take rigorous precautions with capsule contents to avoid inhalation or contact with the skin or mucous membranes. In case of powder contact, the hands should be washed. *[see Dosage and Administration (2.3)]* .

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1)]* .

Advise females of reproductive potential to use effective contraception during treatment with temozolomide and for at least 6 months after the last dose *[see Use in Specific Populations (8.3)]* .

Advise male patients with pregnant partners or female partners of reproductive potential to use condoms during treatment with temozolomide and for at least 3 months after the final dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]* .

Advise male patients not to donate semen during treatment with temozolomide and for at least 3 months after the final dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]* .

Lactation
Advise women not to breastfeed during treatment with temozolomide and for at least 1 week after the final dose *[see Use in Specific Populations (8.2)]* .

Infertility
Advise males of reproductive potential that temozolomide may impair fertility *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]* .

Manufactured For:
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Manufactured By:
Intas Pharmaceuticals Limited,
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Issued March 2020

Pharmacist: Tear at perforations and give to patients

Patient Information

Temozolomide capsules

(TEM-oh-ZOE-loe-mide)

What is the most important information I should know about temozolomide capsules?
Temozolomide capsules may cause birth defects.
Females and female partners of male patients who take temozolomide capsules:

- Avoid becoming pregnant while taking temozolomide capsules.
- Females who can become pregnant should use an effective form of birth control (contraception) during treatment and for at least 6 months after your last dose of temozolomide capsules. Your doctor should to do a pregnancy test to make sure that you are not pregnant before you start taking temozolomide capsules.
- Tell your doctor right away if you become pregnant or think you are pregnant during treatment with temozolomide capsules.

Males taking temozolomide capsules and have a female partner who is pregnant or who can become pregnant:

- Use a condom for birth control (contraception) during treatment and for at least 3 months after taking your final dose of temozolomide capsules.
- Do not donate semen during treatment and for at least 3 months after your final dose of temozolomide capsules.

See the section "What are the possible side effects of temozolomide capsules?" for more information about side effects.

What is temozolomide capsule?

Temozolomide capsule is a prescription medicine used to treat adults with certain brain cancer tumors. It is not known if temozolomide capsule is safe and effective in children.

Who should not take temozolomide capsules?

Do not take temozolomide capsule if you:

- have had an allergic reaction to temozolomide or any of the other ingredients in temozolomide capsules. See the end of this leaflet for a list of ingredients in temozolomide capsules. Symptoms of an allergic reaction with temozolomide capsules may include: a red itchy rash, or a severe allergic reaction, such as trouble breathing, swelling of the face, throat, or tongue, or severe skin reaction. If you are not sure, ask your doctor.
- have had an allergic reaction to dacarbazine (DTIC), another cancer medicine.

What should I tell my doctor before taking temozolomide capsules?

Tell your doctor about all of your medical conditions, including if you:

- have kidney problems
- have liver problems
- are pregnant or plan to become pregnant. **See "What is the most important information I should know about temozolomide capsules?"**
- are breast-feeding or plan to breastfeed. It is not known if temozolomide passes into your breast milk. **Do not** breastfeed during treatment and for at least 1 week after your last dose of temozolomide capsules.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take a medicine that contains valproic acid.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take temozolomide capsules?

Temozolomide capsules may be taken by mouth as a capsule.
Your doctor will decide the best way for you to take temozolomide capsules. Take temozolomide capsules exactly as prescribed by your doctor.

There are 2 common dosing schedules for taking temozolomide capsules depending on the type of brain cancer tumor that you have.

- People with certain brain can cancer tumors take or receive temozolomide capsules:
  - 1 time each day for 42 days in a row (possibly 49 days depending on side effects) along with receiving radiation treatment. **This is 1 cycle of treatment.**
  - After this, your doctor may prescribe 6 more cycles of temozolomide capsules as "maintenance" treatment. For each of these cycles, you take or receive temozolomide capsules 1 time each day for 5 days in a row and then you stop taking it for the next 23 days. **This is a 28-day**

maintenance treatment cycle.

- People with certain other brain cancer tumors take or receive temozolomide capsules:
  - 1 time each day for 5 days in a row only, and then stop taking it for the next 23 days. **This is 1 cycle of treatment (28 days).**
  - Your doctor will watch your progress on temozolomide capsules and decide how long you should take it. You might take temozolomide capsules until your tumor gets worse or for possibly up to 2 years.
- If your doctor prescribes a treatment regimen that is different from the information in this leaflet, make sure you follow the instructions given to you by your doctor.
- Your doctor may change your dose of temozolomide capsules, or tell you to stop temozolomide capsules for a short period of time or permanently if you have certain side effects.
- Your doctor will decide how many treatment cycles of temozolomide capsules that you will receive, depending on how you respond to and tolerate treatment.

Temozolomide capsules:

- Take temozolomide capsules exactly as your doctor tells you to.
- Temozolomide capsules come in different strengths. Each strength has a different color cap. Your doctor may prescribe more than 1 strength of temozolomide capsules for you, so it is important that you understand how to take your medicine the right way. Be sure that you understand exactly how many capsules you need to take on each day of your treatment, and what strengths to take. **This may be different whenever you start a new cycle.**
- **Do not** take more temozolomide capsules than prescribed.
- Talk to your doctor or pharmacist before taking your dose if you are not sure how much temozolomide capsules to take. This will help to prevent taking too much temozolomide capsules and decrease your chances of getting serious side effects.
- Take each day's dose of temozolomide capsules at one time, with a full glass of water.
- **Swallow temozolomide capsules whole.** Do not chew, open, or split the capsules.
- Take temozolomide capsules at the same time each day.
- Take temozolomide capsules the same way each time, either with food or without food.
- If temozolomide capsules are accidentally opened or damaged, be careful not to breathe in (inhale) the powder from the capsules or get the powder on your skin or mucous membranes (for example, in your nose or mouth). If contact with any of these areas happens, flush the area with water.
- To help reduce nausea and vomiting, try to take temozolomide capsules on an empty stomach or at bedtime. Your doctor may prescribe medicine to help prevent or treat nausea, or other medicines to reduce side effects with temozolomide capsules.
- See your doctor regularly to check your progress. Your doctor will check you for side effects.
- If you take more temozolomide capsules than prescribed, call your doctor or get emergency medical help right away.

What are the possible side effects of temozolomide capsules?

Temozolomide capsules can cause serious side effects, including:

- **See "What is the most important information I should know about temozolomide capsules?"**
- **Decreased blood cell counts.** Temozolomide capsules can affect your bone marrow and cause you to have decreased blood cell counts. Decreased white blood cell count, red blood cell count and platelet count are common with temozolomide capsules but it can also be severe and lead to death.
  - Your doctor will do blood tests regularly to check your blood cell counts before you start and during treatment with temozolomide capsules.
  - Your doctor may need to change the dose of temozolomide capsules, or when you get it depending on your blood cell counts.
  - **People who are age 70 or older and women have a higher risk for developing decreased blood cell counts during treatment with temozolomide capsules.**
- **Secondary cancers.** Blood problems such as myelodysplastic syndrome (MDS) and new cancers

(secondary cancers), including a certain kind of leukemia, can happen in people who take temozolomide capsules. Your doctor will monitor you for this.

- **Pneumocystis pneumonia (PCP).** PCP is an infection that people can get when their immune system is weak. Temozolomide capsules decreases white blood cells, which makes your immune system weaker and can increase your risk of getting PCP.
  - People who are taking steroid medicines or who stay on temozolomide capsules for a longer period of time may have an increased risk of getting PCP infection.
  - Anyone who takes temozolomide capsules will be watched carefully by their doctor for low blood cell counts and this infection.
  - Tell your doctor if you have any of the following signs and symptoms of PCP infection: shortness of breath, or fever, chills, dry cough.
- **Liver problems. Liver problems can happen with temozolomide capsules and can sometimes be severe and lead to death.** Your doctor will do blood tests to check your liver function before you start taking temozolomide capsules, during treatment, and about 2 to 4 weeks after your last dose of temozolomide capsules.

Common side effects of temozolomide capsules include:

- hair loss
- feeling tired
- nausea and vomiting.
- headache
- constipation
- loss of appetite
- convulsions
- rash
- diarrhea
- unable to move (paralysis) on one side of the body
- weakness
- fever
- dizziness
- coordination problems
- viral infection
- memory loss
- sleep problems

Temozolomide capsules can affect fertility in males and may affect your ability to father a child. Talk with your doctor if fertility is a concern for you.
These are not all the possible side effects with temozolomide capsules. For more information, ask your doctor or pharmacist.

These are not all the possible side effects with temozolomide capsules. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store temozolomide capsules?

- Store temozolomide capsules at 77°F (controlled room temperature). Storage at 59°F to 86°F (15°C to 30°C) is permitted occasionally.
- Temozolomide capsules comes in a child-resistant package.
- **Keep temozolomide capsules and all medicines out of the reach of children.**

General information about the safe and effective use of temozolomide capsules.

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use temozolomide capsules for a condition for which it was not prescribed. Do not give temozolomide capsules to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about temozolomide capsules. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about temozolomide capsules that is written for health professionals.

For more information, go to *www.accordhealthcare.us* or call Accord Healthcare at 1-866-941-7875.

What are the ingredients in temozolomide capsules?
Temozolomide capsules:

Active ingredient: temozolomide.
Inactive ingredients: lactose anhydrous, colloidal anhydrous silica, sodium starch glycolate, tartaric acid, stearic acid.

The body of the capsules is made of gelatin and is white. The body of 250 mg capsule contain additionally sodium lauryl sulfate. The cap is also made of gelatin, and the colors vary based on the dosage strength. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains black iron oxide, potassium hydroxide and shellac.

Temozolomide capsules 5 mg: The green cap contains gelatin, titanium dioxide, iron oxide yellow and FD&C Blue 2.

Temozolomide capsules 20 mg: The yellow cap contains gelatin, iron oxide yellow and titanium dioxide.

Temozolomide capsules 100 mg: The pink cap contains gelatin, titanium dioxide and iron oxide red.

Temozolomide capsules 140 mg: The transparent blue cap contains gelatin and FD&C Blue 2.

Temozolomide capsules 180 mg: The maroon cap contains gelatin, iron oxide red, iron oxide yellow and titanium dioxide.

Temozolomide capsules 250 mg: The white cap contains gelatin, titanium dioxide and sodium lauryl sulfate.

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10 1475 3 6000974

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Temozolomide Capsules

PHARMACIST:
Dispense enclosed Patient Package Insert to each patient.

PHARMACIST INFORMATION SHEET

IMPORTANT DISPENSING INFORMATION

For every patient, temozolomide capsules must be dispensed in a separate vial or in its original package making sure each container lists the strength per capsule and that patients take the appropriate number of capsules from each package or vial.

Please see the dispensing instructions below for more information.

What is temozolomide capsule?

Temozolomide is an oral alkylating agent for the treatment of newly diagnosed glioblastoma multiforme and refractory anaplastic astrocytoma.

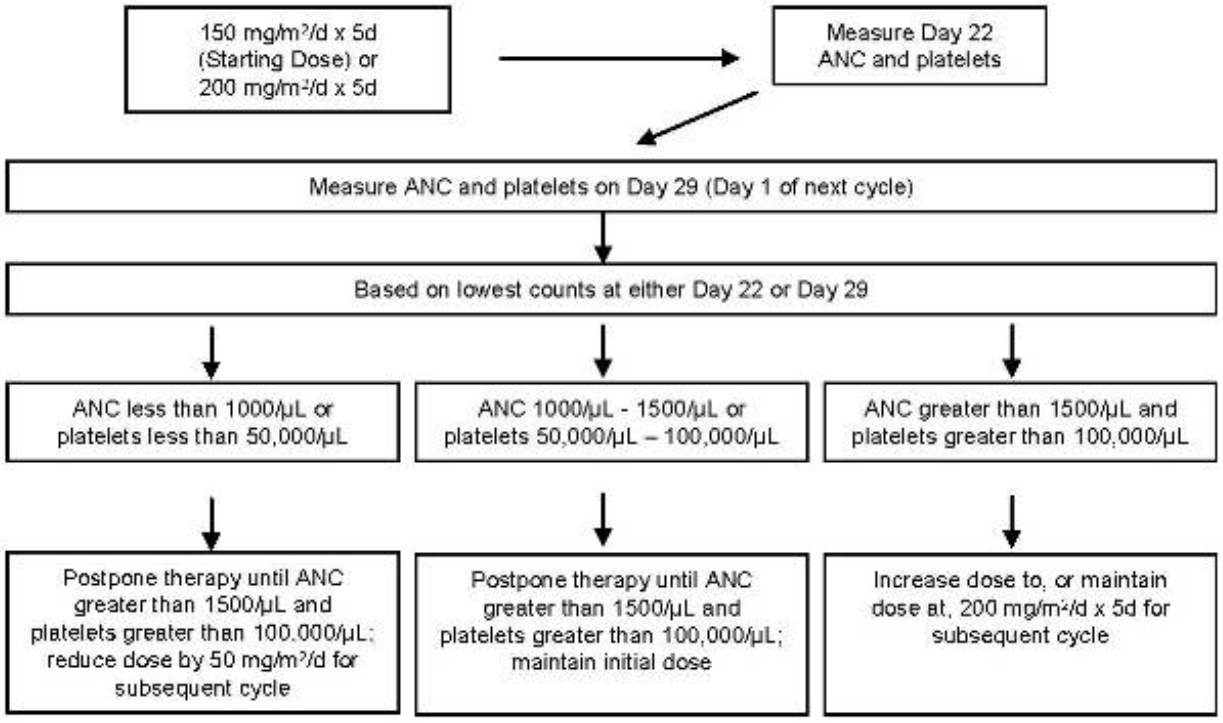
How is temozolomide capsules dosed?

The daily dose of temozolomide capsules for a given patient is calculated by the physician, based on the patient's body surface area (BSA). The resulting dose is then rounded off to the nearest 5 mg. An example of the dosing may be as follows: the initial daily dose of temozolomide capsules in milligrams is the BSA multiplied by mg/m^2/day, (a patient with a BSA of 1.84 is 1.84 x 75 mg = 138, or 140 mg/day). The dose for subsequent cycles may be adjusted according to nadir neutrophil and platelet counts in the previous cycle and at the time of initiating the next cycle.

How might the dose of temozolomide capsules be modified for Refractory Anaplastic Astrocytoma?

Dosage of temozolomide capsules must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and neutrophil and platelet counts at the time of initiating the next cycle. The initial dose is 150 mg/m^2 orally once daily for 5 consecutive days per 28-day treatment cycle. If both the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil counts (ANC) are greater than or equal to 1.5 x 10^9/L (1500/µL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are greater than or equal to 100 x 10^9/L (100,000/µL), the temozolomide capsules dose may be increased to 200 mg/m^2/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1500/µL) and the platelet count exceeds 100 x 10^9/L (100,000/µL). The next cycle of temozolomide capsules should not be started until the ANC and platelet count exceed these levels. If the ANC falls to less than 1.0 x 10^9/L (1000/µL) or the platelet count is less than 50 x 10^9/L (50,000/µL) during any cycle, the next cycle should be reduced by 50 mg/m^2, but not below 100 mg/m^2, the lowest recommended dose (see **Table 1** below)

TABLE 1: Dosing Modification Table for Refractory Anaplastic Astrocytoma



What is the temozolomide capsules treatment regimen?

Temozolomide capsules are given for 5 consecutive days on a 28-day cycle. Patients should continue taking temozolomide capsules until their physician determines that their disease has progressed, up to 2 years, or until unacceptable side effects or toxicities occur. Physicians may alter the treatment regimen for a given patient.

Newly Diagnosed Concomitant Phase Treatment Schedule

Temozolomide capsules are administered orally at 75 mg/m ^{2} daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions), followed by maintenance temozolomide capsules for 6 cycles. No dose reductions are recommended; however, dose interruptions may occur based on patient tolerance. The temozolomide capsules dose can be continued throughout the 42 day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count greater than or equal to 1.5 x 10 ^{9}/L, platelet count greater than or equal to 100 x10 ^{9}/L, common toxicity criteria (CTC) nonhematological toxicity less than or equal to Grade 1 (except for alopecia, nausea and vomiting). During treatment a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and nonhematological toxicity criteria as noted in **Table 2**. Pneumocystis carinii pneumonia (PCP) prophylaxis is required during the concomitant administration of temozolomide and radiotherapy, and should be continued in patients who develop lymphocytopenia until recovery from lymphocytopenia (CTC grade less than or equal to 1).

TABLE 2: Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

Toxicity	**TMZ Interruption** *	**TMZ Discontinuation**
Absolute Neutrophil Count	greater than or equal to	less than 0.5 x 10 ^{9}/L

	0.5 and less than 1.5 x 10^9/L	
Platelet Count	greater than or equal to 10 and less than 100 x 10^9/L	less than 10 x 10^9/L
CTC Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

TMZ = temozolomide; CTC = Common Toxicity Criteria.

* Treatment with concomitant TMZ could be continued when all of the following conditions were met: absolute neutrophil count greater than or equal to 1.5 x 10 9/L; platelet count greater than or equal to 100 x 10 9/L; CTC nonhematological toxicity less than or equal to Grade 1 (except for alopecia, nausea, vomiting).

Maintenance Phase Treatment Schedule

Four weeks after completing the temozolomide + RT phase, temozolomide capsules are administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m^2, if the CTC nonhematologic toxicity for Cycle 1 is Grade less than or equal to 2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is greater than or equal to 1.5 x 10^9/L, and the platelet count is greater than or equal to 100 x 10^9/L. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. The dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs.

During treatment a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1500/µL) and the platelet count exceeds 100 x 10^9/L (100,000/µL). The next cycle of temozolomide capsules should not be started until the ANC and platelet count exceed these levels. Dose reductions during the next cycle should be based on the lowest blood counts and worst nonhematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to Tables **3** and **4**.

TABLE 3: Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m^2/day)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

TABLE 4: Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

Toxicity	Reduce TMZ by 1 Dose Level *	Discontinue TMZ
Absolute Neutrophil Count	less than 1.0 x 10^9/L	See footnote †
Platelet Count	less than 50 x 10^9/L	See footnote †

CTC Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4 †

TMZ = temozolomide; CTC = Common Toxicity Criteria.

* TMZ dose levels are listed in Table 3.

† TMZ is to be discontinued if dose reduction to less than 100 mg/m 2 is required or if the same Grade 3 nonhematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

How is temozolomide capsules taken?

Patients should take each day's dose with a full glass of water at the same time each day. Taking the medication on an empty stomach or at bedtime may help ease nausea. If patients are also taking antinausea or other medications to relieve the side effects associated with temozolomide, they should be advised to take these medications 30 minutes before they take temozolomide capsules. Temozolomide causes the rapid appearance of malignant tumors in rats. Patients **SHOULD NOT** open or split the capsules. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. The medication should be kept away from children and pets. The temozolomide capsules should be swallowed whole and **NEVER CHEWED**.

What should the patient avoid during treatment with temozolomide capsules?

There are no dietary restrictions for patients taking temozolomide capsules. Temozolomide capsules may affect testicular function, so male patients should exercise adequate birth control measures. Temozolomide capsules may cause birth defects. Female patients should avoid becoming pregnant while receiving this drug. Women who are nursing prior to receiving temozolomide capsules should discontinue nursing. It is not known whether temozolomide is excreted into breast milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants and tumorigenicity shown for temozolomide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of temozolomide capsules to the mother.

What are the side effects of temozolomide capsules?

Nausea and vomiting are the most common side effects associated with temozolomide capsules. Noncumulative myelosuppression is the dose-limiting toxicity. Patients should be evaluated periodically by their physician to monitor blood counts.

Other commonly reported side effects reported by patients taking temozolomide capsules are fatigue, constipation, alopecia, anorexia, and headache.

How is temozolomide capsules supplied?

Temozolomide capsules are available in 5-mg, 20-mg, 100-mg, 140-mg, 180-mg, and 250-mg strengths. The capsules contain a white capsule body with a color cap, and the colors vary based on the dosage strength.

Temozolomide Capsule Strength	**Color**
5 mg	Green Cap
20 mg	Yellow Cap
100 mg	Pink Cap
140 mg	Transparent Blue Cap

180 mg	Maroon Cap
250 mg	White Cap

The 5-mg, 20-mg, 100-mg, 140-mg, and 180-mg capsule strengths are available in 5 count and 14 count packages. The 250-mg capsule strengths are available in 5 count package.

How is temozolomide capsules dispensed?

Each strength of temozolomide capsules must be dispensed in a separate vial or in its original package (one strength per one container). Follow the instructions below:

Based on the dose prescribed, determine the number of each strength of temozolomide capsules needed for the full 42-or 5-day cycle as prescribed by the physician. For example, in a 5-day cycle, 275 mg/day would be dispensed as five 250-mg capsules, five 20-mg capsules and five 5-mg capsules. Label each container with the appropriate number of capsules to be taken each day. Dispense to the patient, making sure each container lists the strength (mg) per capsule and that he or she understands to take the appropriate number of capsules of temozolomide from each package or vial to equal the total daily dose prescribed by the physician.

How can temozolomide capsules be ordered?

Temozolomide capsules can be ordered from your wholesaler. It is important to understand if temozolomide capsules are being used as part of a 42-day regimen or as part of a 5-day course. Remember to order enough temozolomide capsules for the appropriate cycle. For example:

- a 5-day course of 360 mg/day would require the following to be ordered: two 5-count packages of 180-mg capsules.
- a 42-day course of 140 mg/day would require the following to be ordered: three 14-count packages of 140-mg capsules.

For examples of other dosing regimens, please refer to the full **Prescribing Information (Table 6).**

Temozolomide Capsules	**NDC Number**
Amber Glass Bottles:	
5-mg capsules (5 count)	16729-048-53
5-mg capsules (14 count)	16729-048-54
20-mg capsules (5 count)	16729-049-53
20-mg capsules (14 count)	16729-049-54
100-mg capsules (5 count)	16729-050-53
100-mg capsules (14 count)	16729-050-54
140-mg capsules (5 count)	16729-129-53
140-mg capsules (14 count)	16729-129-54
180-mg capsules (5 count)	16729-130-53
180-mg capsules (14 count)	16729-130-54
250-mg capsules (5 count)	16729-051-53
Sachet Packs (Carton Contains Individual Sachet with One Capsule each):	
5-mg capsules (5 count)	16729-048-31
5-mg capsules (14 count)	16729-048-04
20-mg capsules (5 count)	16729-049-31
20-mg capsules (14 count)	16729-049-04
100-mg capsules (5 count)	16729-050-31
100-mg capsules (14 count)	16729-050-04
140-mg capsules (5 count)	16729-129-31

140-mg capsules (14 count)	16729-129-04
180-mg capsules (5 count)	16729-130-31
180-mg capsules (14 count)	16729-130-04
250-mg capsules (5 count)	16729-051-31

Manufactured For:
Accord Healthcare, Inc.,
1009 Slater Road,
Suite 210-B,
Durham, NC 27703,
USA.

Manufactured By:
Intas Pharmaceuticals Limited,
Ahmedabad – 380 054, India.

10 1475 3 6000974

Issued March 2020

PRINCIPAL DISPLAY PANEL

Principal Display Panel- 5 mg Capsules

Amber Glass Bottle Carton

NDC 16729- **048**-53

Temozolamide
Capsules

5 mg

Rx only

5 capsules

Principal Display Panel- 20 mg Capsules

Amber Glass Bottle Carton

NDC 16729- **049**-53

Temozolamide
Capsules

20 mg

Rx only

5 capsules

Principal Display Panel- 100 mg Capsules

Amber Glass Bottle Carton

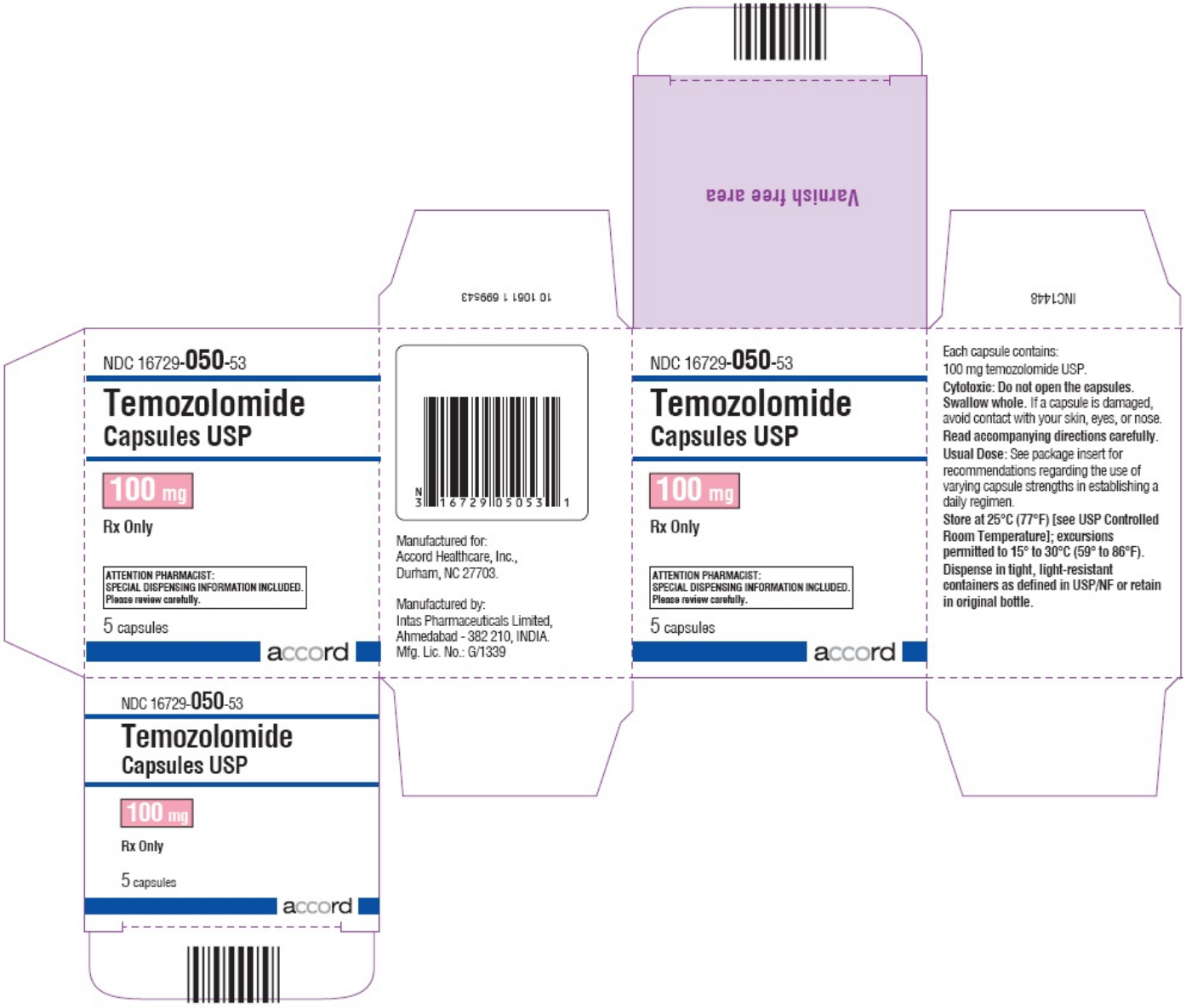
NDC 16729- **050**-53

Temozolamide
Capsules

100 mg

Rx only

5 capsules



Principal Display Panel- 140 mg Capsules

Amber Glass Bottle Carton

NDC 16729- **129**-53

Temozolamide
Capsules

140 mg

Rx only

5 capsules

Principal Display Panel- 180 mg Capsules

Amber Glass Bottle Carton

NDC 16729- **130**-53

Temozolamide
Capsules

180 mg

Rx only

5 capsules

Principal Display Panel- 250 mg Capsules

Amber Glass Bottle Carton

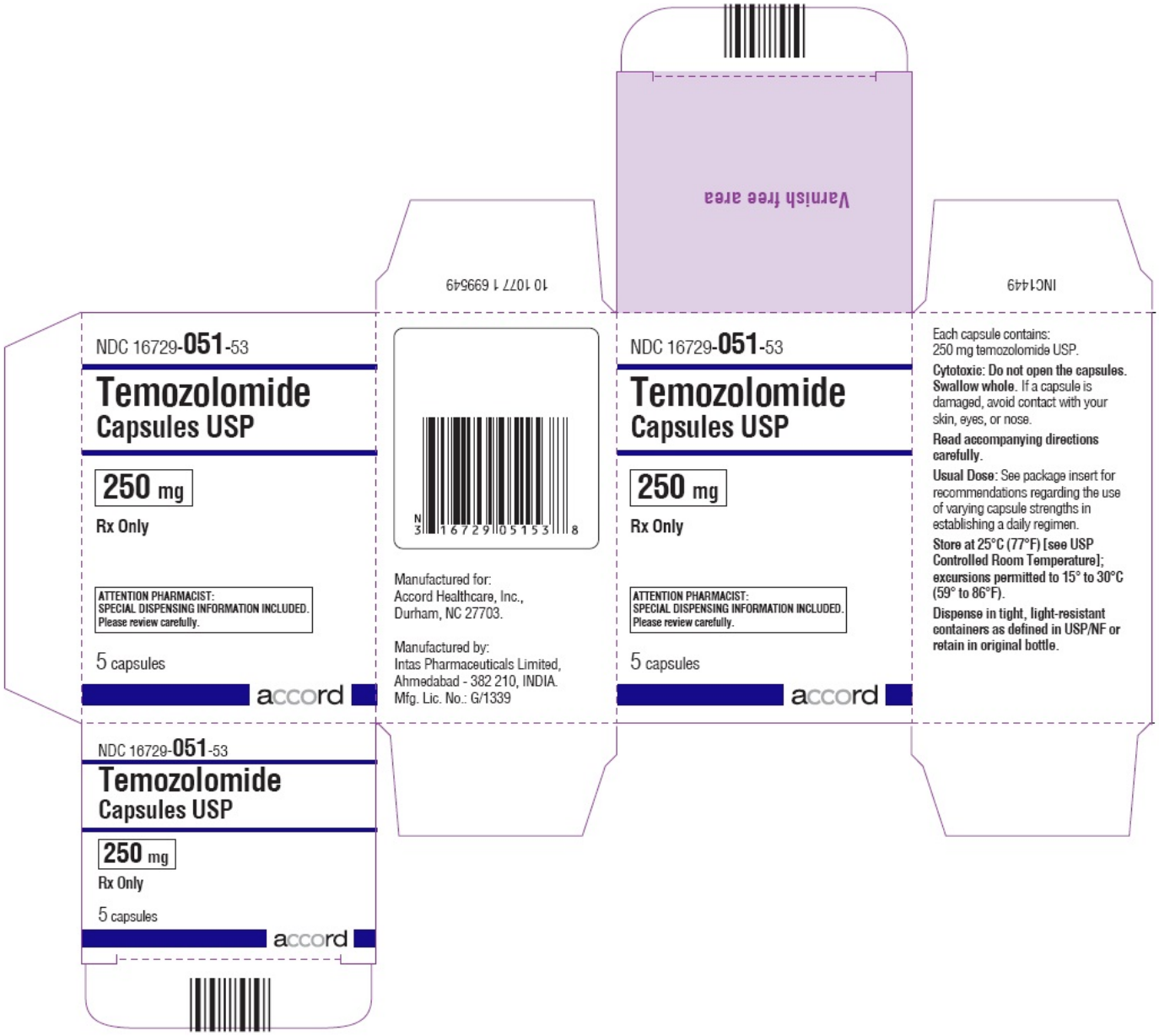
NDC 16729- **051**-53

Temozolamide
Capsules

250 mg

Rx only

5 capsules



Principal Display Panel- 5 mg Capsules

Sachet Pack Carton

NDC 16729- **048**-31

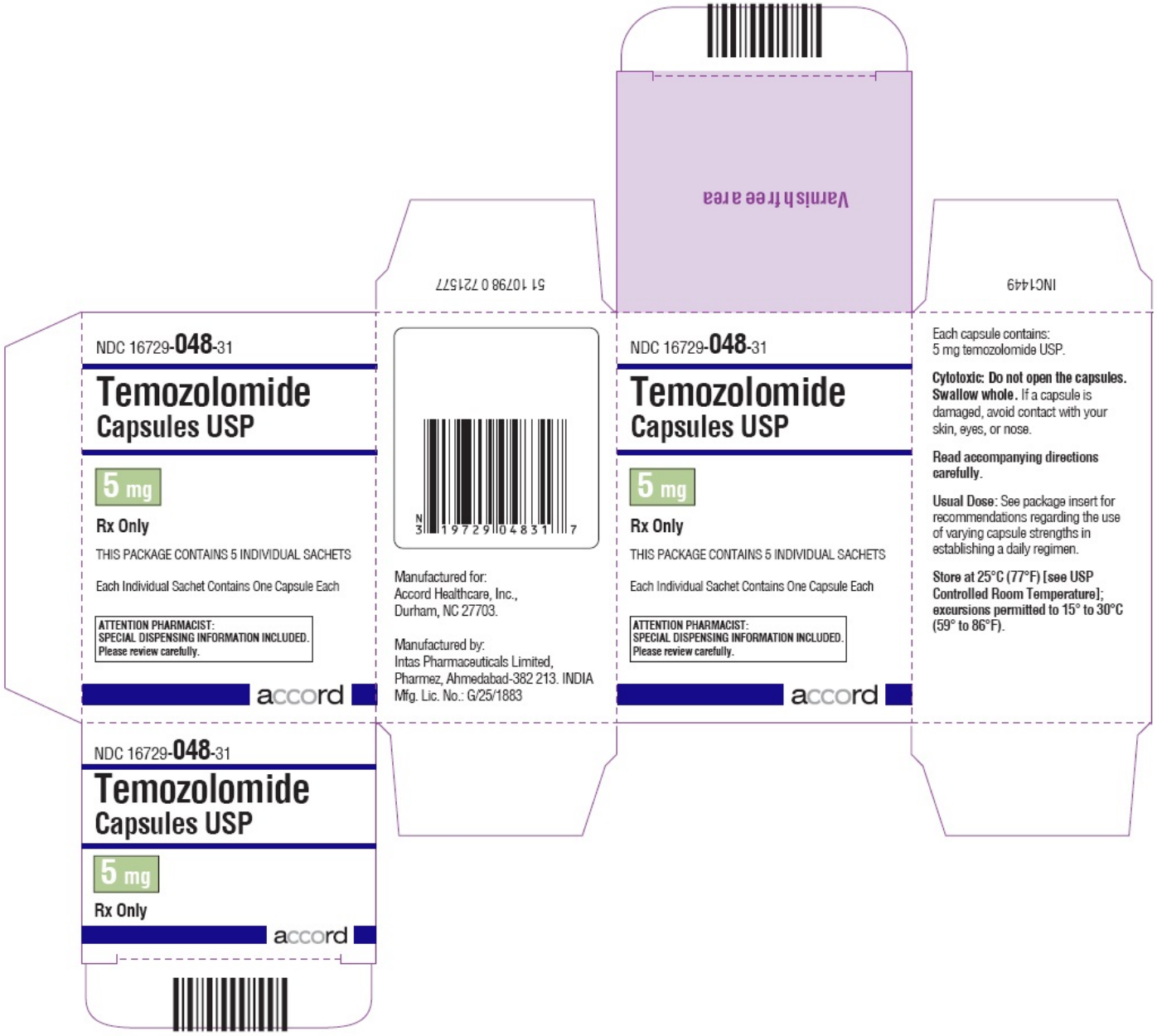
Temozolamide
Capsules

5 mg

Rx only

THIS PACKAGE CONTAINS 5 INDIVIDUAL SACHETS

Each Individual Sachet Contains One Capsule Each



Principal Display Panel- 20 mg Capsules

Sachet Pack Carton

NDC 16729- **049**-31

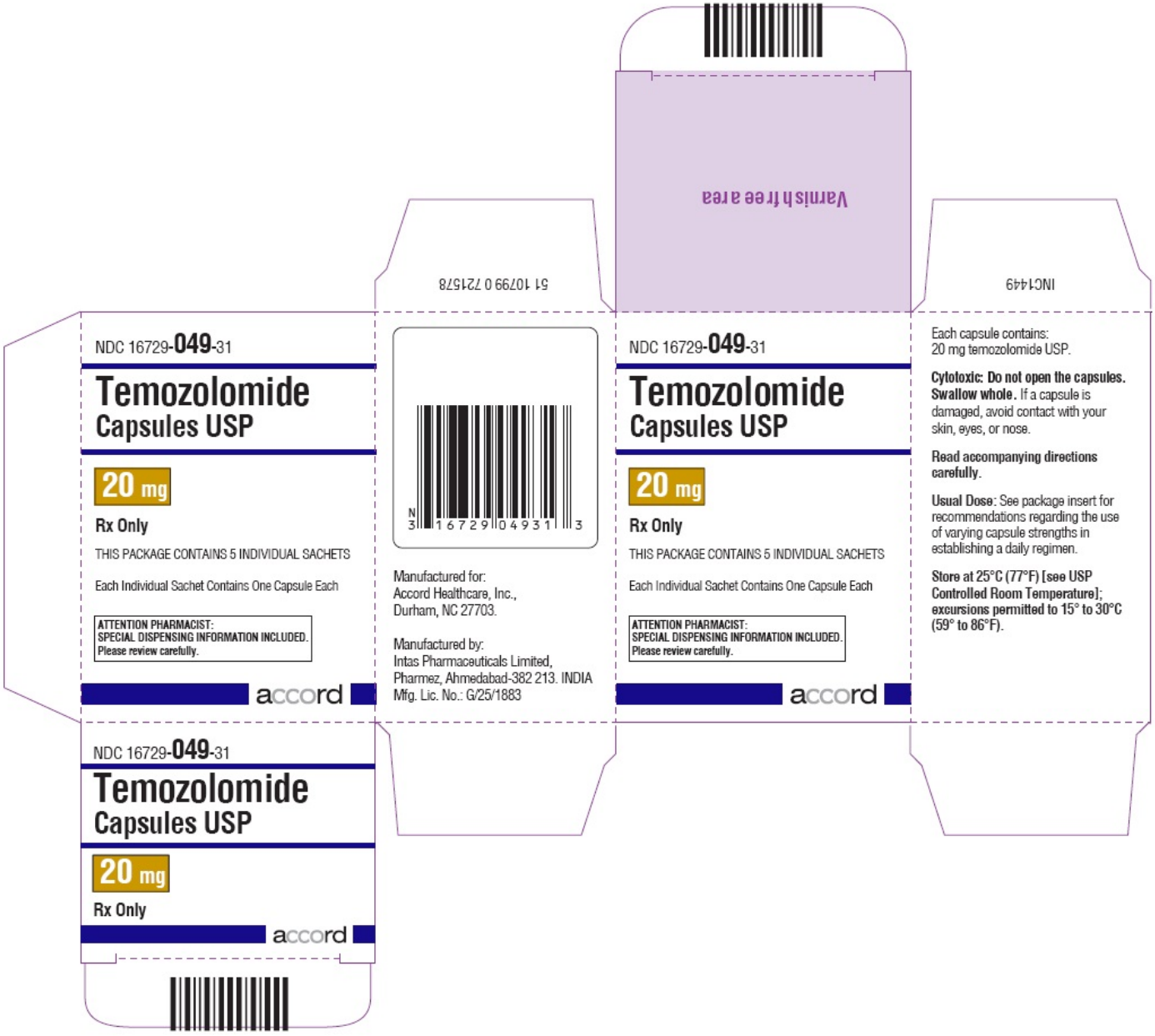
Temozolamide
Capsules

20 mg

Rx only

THIS PACKAGE CONTAINS 5 INDIVIDUAL SACHETS

Each Individual Sachet Contains One Capsule Each



Principal Display Panel- 100 mg Capsules

Sachet Pack Carton

NDC 16729- **050**-31

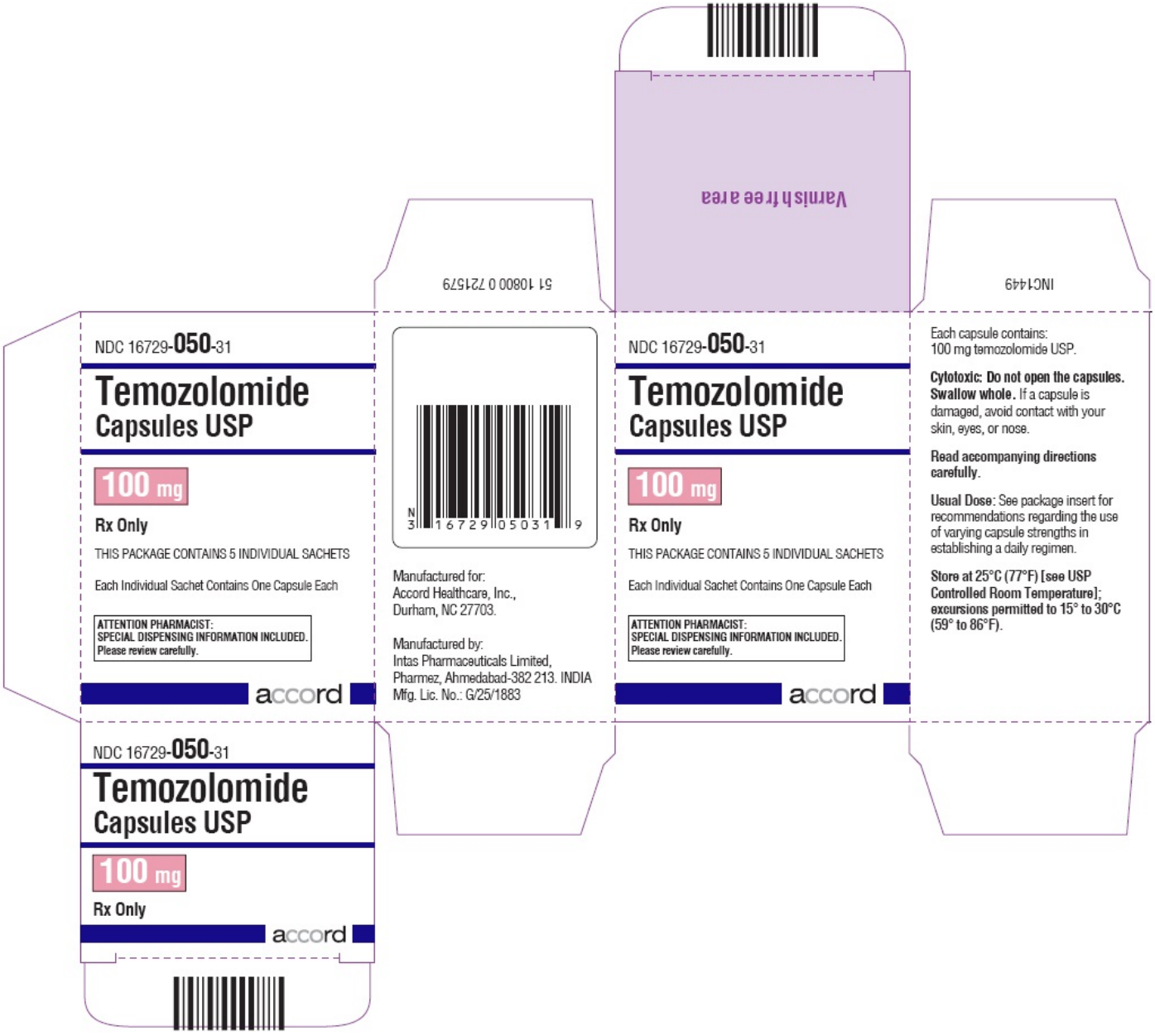
Temozolamide
Capsules

100 mg

Rx only

THIS PACKAGE CONTAINS 5 INDIVIDUAL SACHETS

Each Individual Sachet Contains One Capsule Each



Principal Display Panel- 140 mg Capsules

Sachet Pack Carton

NDC 16729- **129**-31

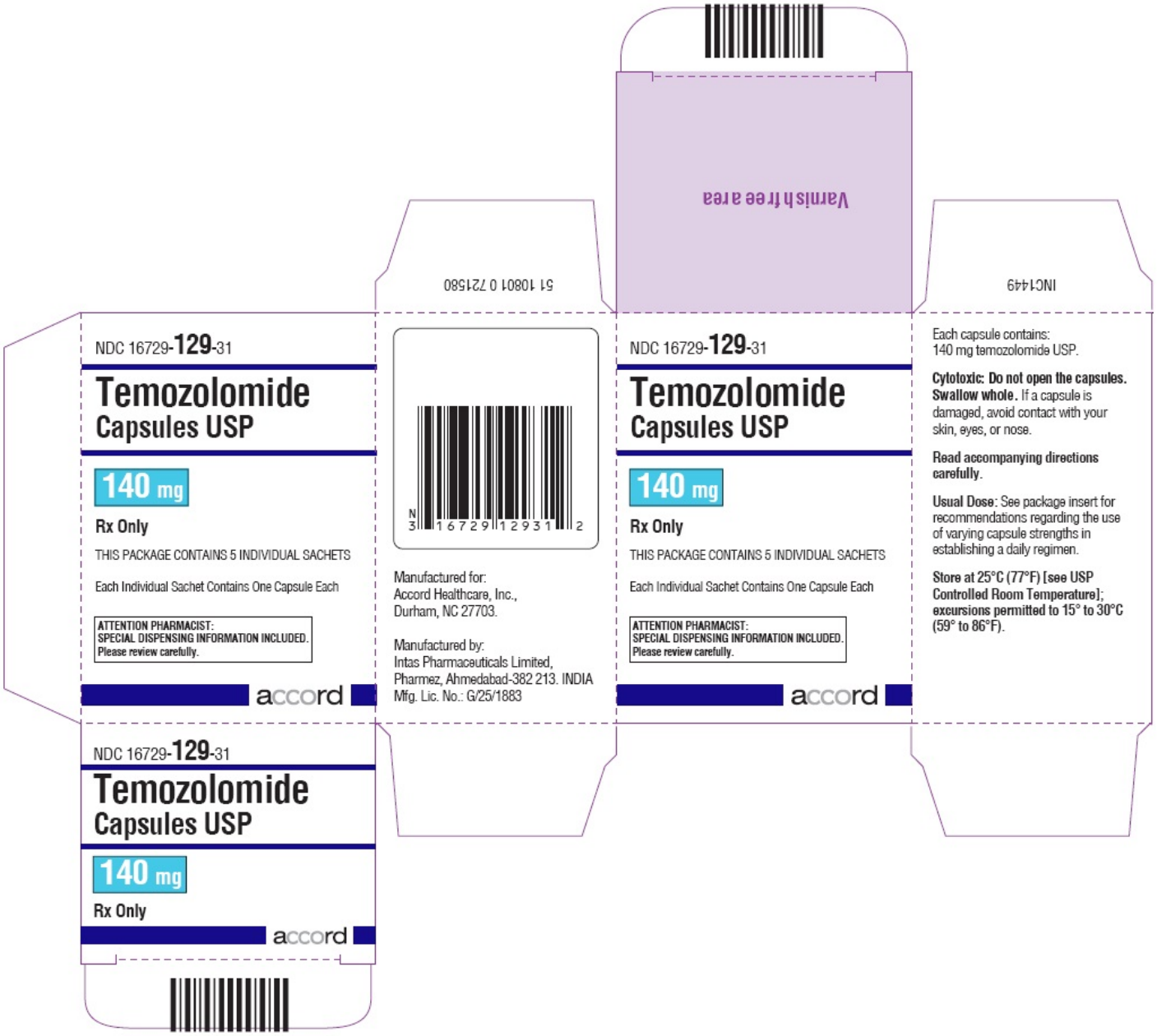
Temozolamide
Capsules

140 mg

Rx only

THIS PACKAGE CONTAINS 5 INDIVIDUAL SACHETS

Each Individual Sachet Contains One Capsule Each



Principal Display Panel- 180 mg Capsules

Sachet Pack Carton

NDC 16729- **130**-31

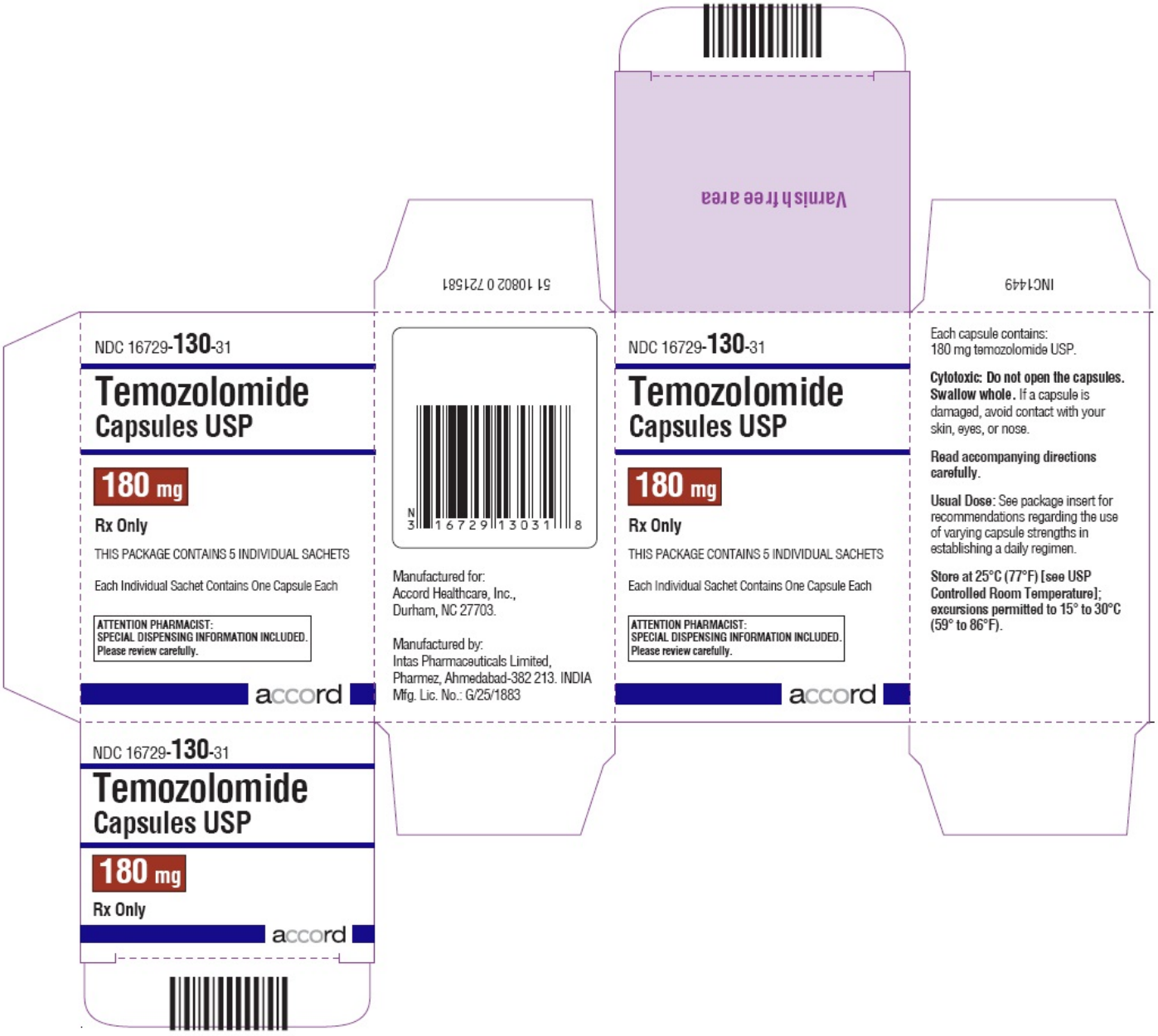
Temozolamide
Capsules

180 mg

Rx only

THIS PACKAGE CONTAINS 5 INDIVIDUAL SACHETS

Each Individual Sachet Contains One Capsule Each



Principal Display Panel- 250 mg Capsules

Sachet Pack Carton

NDC 16729- **051**-31

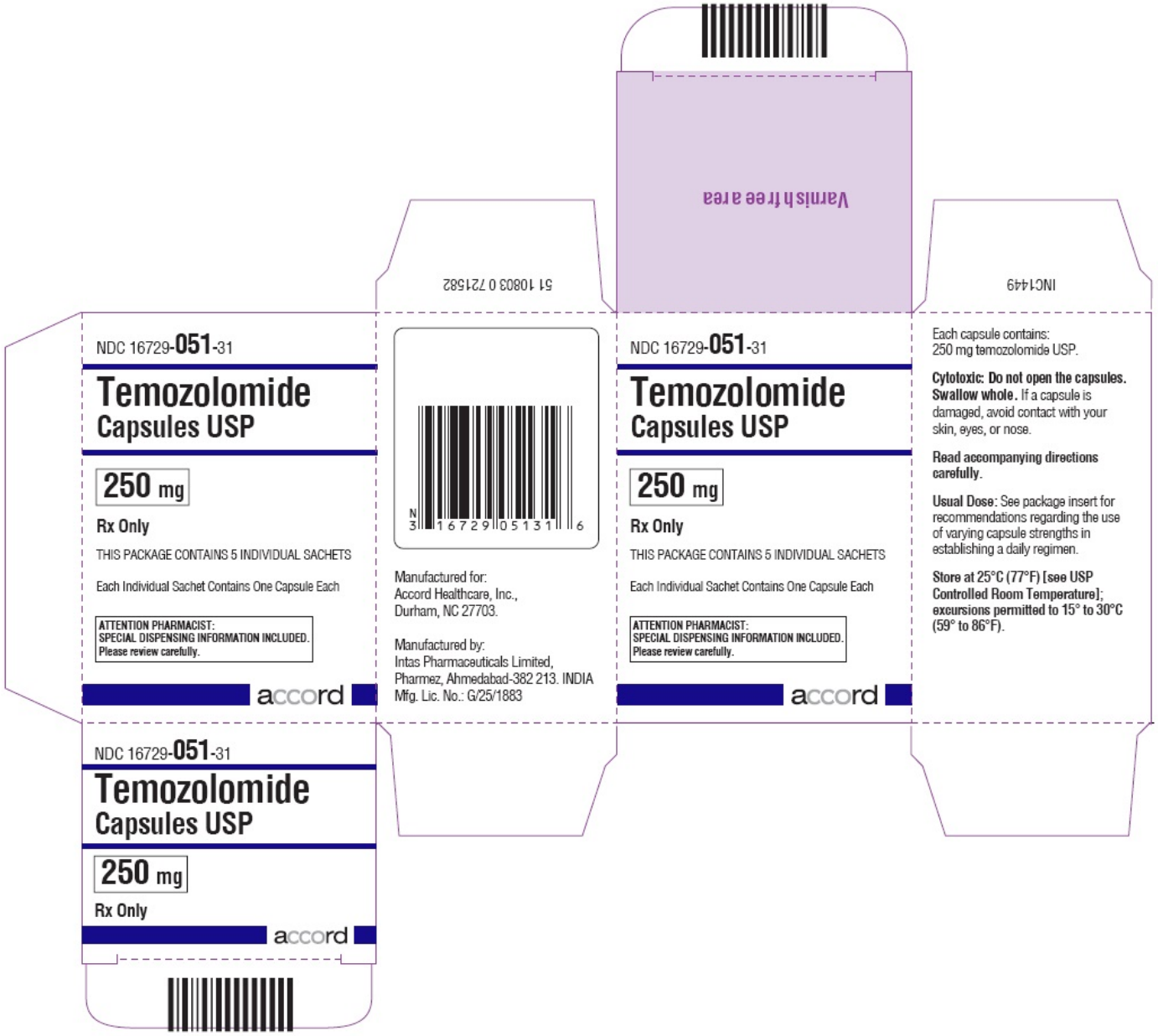
Temozolamide
Capsules

250 mg

Rx only

THIS PACKAGE CONTAINS 5 INDIVIDUAL SACHETS

Each Individual Sachet Contains One Capsule Each



TEMOZOLOMIDE

temozolomide capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:16729-048
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	5 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TARTARIC ACID (UNII: W4888I119H)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
SHELLAC (UNII: 46N107B71O)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics

Color	green, white	**Score**	no score
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	5;TMZ
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:16729-048-53	1 in 1 CARTON	03/07/2017	
1		5 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product		
2	NDC:16729-048-54	1 in 1 CARTON	03/07/2017	
2		14 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product		
3	NDC:16729-048-31	5 in 1 CARTON	11/20/2024	
3		1 in 1 POUCH; Type 0: Not a Combination Product		
4	NDC:16729-048-04	14 in 1 CARTON	11/20/2024	
4		1 in 1 POUCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201528	03/07/2017	

TEMOZOLOMIDE

temozolomide capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:16729-049
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	20 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TARTARIC ACID (UNII: W4888I119H)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
SHELLAC (UNII: 46N107B71O)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics

Color	yellow, white	**Score**	no score
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	20;TMZ
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
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2		14 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product		
3	NDC:16729-049-31	5 in 1 CARTON	11/20/2024	
3		1 in 1 POUCH; Type 0: Not a Combination Product		
4	NDC:16729-049-04	14 in 1 CARTON	11/20/2024	
4		1 in 1 POUCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201528	03/07/2017	

TEMOZOLOMIDE

temozolomide capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:16729-050
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	100 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TARTARIC ACID (UNII: W4888I119H)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics

Color	pink, white	**Score**	no score
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	100;TMZ
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
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2	NDC:16729-050-54	1 in 1 CARTON	03/07/2017	

2		14 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product		
3	NDC:16729-050-31	5 in 1 CARTON	11/20/2024	
3		1 in 1 POUCH; Type 0: Not a Combination Product		
4	NDC:16729-050-04	14 in 1 CARTON	11/20/2024	
4		1 in 1 POUCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201528	03/07/2017	

TEMOZOLOMIDE

temozolomide capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:16729-129
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	140 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TARTARIC ACID (UNII: W4888I119H)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
SHELLAC (UNII: 46N107B71O)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics

Color	blue, white	**Score**	no score
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	140;TMZ
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
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1		5 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product		
2	NDC:16729-129-54	1 in 1 CARTON	03/07/2017	
2		14 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product		
3	NDC:16729-129-31	5 in 1 CARTON	11/20/2024	
3		1 in 1 POUCH; Type 0: Not a Combination Product		
4	NDC:16729-129-04	14 in 1 CARTON	11/20/2024	
4		1 in 1 POUCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201528	03/07/2017	

TEMOZOLOMIDE

temozolomide capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:16729-130
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	180 mg

Inactive Ingredients	
Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TARTARIC ACID (UNII: W4888I119H)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
SHELLAC (UNII: 46N107B71O)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics			
Color	orange (maroon) , white	**Score**	no score
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	180;TMZ
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:16729-130-53	1 in 1 CARTON	03/07/2017	
1		5 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product		
2	NDC:16729-130-54	1 in 1 CARTON	03/07/2017	
2		14 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product		
3	NDC:16729-130-31	5 in 1 CARTON	11/20/2024	
3		1 in 1 POUCH; Type 0: Not a Combination Product		
4	NDC:16729-130-04	14 in 1 CARTON	11/20/2024	
4		1 in 1 POUCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201528	03/07/2017	

TEMOZOLOMIDE

temozolomide capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:16729-051
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	250 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

TARTARIC ACID (UNII: W4888I119H)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SHELLAC (UNII: 46N107B71O)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics

Color	white, white	**Score**	no score
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	250;TMZ
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:16729-051-53	1 in 1 CARTON	03/07/2017	
1		5 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product		
2	NDC:16729-051-31	5 in 1 CARTON	11/20/2024	
2		1 in 1 POUCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201528	03/07/2017	

Labeler - Accord Healthcare Inc. (604222237)

Registrant - Accord Healthcare Inc. (604222237)

Establishment

Name	Address	ID/FEI	Business Operations
Intas Pharmaceuticals Limited		725927649	manufacture(16729-048, 16729-049, 16729-050, 16729-129, 16729-130, 16729-051) , analysis(16729-048, 16729-049, 16729-050, 16729-129, 16729-130, 16729-051)

Establishment

Name	Address	ID/FEI	Business Operations
Intas Pharmaceuticals Limited		915837971	manufacture(16729-048, 16729-049, 16729-050, 16729-129, 16729-130, 16729-051) , analysis(16729-048, 16729-049, 16729-050, 16729-129, 16729-130, 16729-051)

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